Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med 2015;372:426-35. DOI: 10.1056/NEJMoa1409002

Supplementary Appendix

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RESPONSE Investigators

Australia: *Royal Brisbane Hospital, Brisbane*—S. Durrant; *Royal Melbourne Hospital, Parkville*—A. Bajel; *Tweed Hospital, Tweed Heads*—E. Abdi; **Belgium:** *Cliniques Universitaires Saint-Luc, Bruxelles*—L. Knoops; *Gasthuisberg University Hospital, Leuven*—T. Devos; *AZ Sint-Jan, Brugge*—J. Van Droogenbroeck; *ZNA Stuivenberg Hematology and Oncology, Antwerp*—P. Zachee; **Canada:** *Sunnybrook Health Sciences Center, Toronto, ON*—J. Callum; *Princess Margaret Hospital, Toronto, ON*—V. Gupta; *Juravinski Cancer Clinic, Hamilton, ON*—B. Leber; *Jewish General Hospital, Montreal, QC*—J. Prchal; **France:** *Hospital Saint Louis, Paris*—J.-J. Kiladjian; *CHU de Brest—Hopital Morvan, Brest*—J.-C. Ianotto; *Hospital Saint Vincent, Lille*—N. Cambier; *Center Hospitalier d'avignon, Avignon*—B. Slama; *CHU Nancy-Brabois, Vandoeuvre Les Nancy*—D. Ranta; *Hospital Hotel Dieu, Nantes*—V. Dubruille; *Centre Hospitalier de la Cote Basque, Bayonne*—F. Bauduer; **United States:** *Florida Pulmonary Research Institute, Winter Park, FL*—F. Fakih; *Gabrail Cancer Center, Canton, OH*—N. Gabrail; *Alabama Oncology, Birmingham, AL*—J. Harvey; *Palm Beach Institute of Hematology and Oncology, Boynton Beach, FL*—E. Meiri; *Mayo Clinic Arizona, Scottsdale, AZ*—R. Mesa; *Saint Agnes Hospital, Baltimore, MD*—C. Miller; *Fred Hutchinson Cancer Research Center, Seattle, WA*—B. Scott; *Houston Cancer Institute, Houston, TX*—M. Scouros; *Sierra Hematology and Oncology, Sacramento, CA*—C. Spears; *Providence Cancer Institute, Southfield, MI*—H. Terebelo; *The University of Texas MD Anderson Cancer Center, Houston, TX*—S. Verstovsek; *Achieve Clinical Research LLC, Birmingham, AL*—A. Yeilding; *Regional Cancer Care Associates LLC Somerset Division, Somerville, NJ*—S. Young; *Washington University School of Medicine, St Louis, MO*—S. Oh; *Medical University of South Carolina, Charleston, SC*—L. Afrin; *New Hope Cancer and Research Institute, Pomona, CA*—V. Agarwal; *Northwestern University Feinberg School of Medicine, Chicago, IL*—B. Stein; *Sarah Canon Research Institute, Nashville, TN*—J. Berdeja; *Hematology-Oncology Associates of Northern New Jersey and Carol G. Simon Cancer Center, Morristown, NJ*—M. Scola; *University of Nebraska Medical Center, Omaha, NE*—M. Akhtari and S. Rajan; *Florida Cancer Specialists, Fort Myers,*

FL—M.-J. McCleod; *Cancer Center of Acadiana at Lafayette General, Lafayette, LA*—L. Meza; *Capitol Comprehensive Cancer Care Clinic, Jefferson, MO*—A. Khojasteh; *University of Florida College of Medicine at Jacksonville, Jacksonville, FL*—N. Latif; *Sharp Clinical Oncology Research, San Diego, CA*—A. Saleh; *Maine Center for Cancer Medicine and Blood Disorders, Scarborough, ME*—H. Ryan; *Oncology Associates of Bridgeport, Trumbull, CT*—D. Witt; *Geisinger Medical Center Hazelton Cancer Center, Hazelton, PA*—P. Roda; *Maryland Oncology Hematology, P.A., Columbia, MD*—E. Lee; *Cancer Centers of the Carolinas, Greenville, SC*—J. Walls; *Saint Alphonsus Regional Medical Center, Boise, ID*—K. Pulver; *Commonwealth Hematology-Oncology, PC, Lawrence, MA*—P. Sanz-Altamira; **Germany:** *Univ-Klinikum Mannheim Theodor-Kutzer Ufer 1-3, Mannheim*—E. Lengfelder; *Universitatsklinikum Aachen, Aachen*—T. Brümmendorf; *Friedrich-Schiller Universitaetsklinicum Jena, Jena*—A. Hochhaus; *Johannes Wesling Klinikum Minden, Minden*—M. Griesshammer; *Klinikum Rechts der Isar der TU Munchen, Munchen*—P. Jost and J. Duyster; *Univ-Klinik Magdeburg, Magdeburg*—F. Heidel; *Universitaatsklinikum Ulm, Ulm*—K. Döhner; *Universitaetsklinikum Hamburg Eppendorf, Hamburg*—P. Schafhausen; *Charite Berlin Campus Benjamin Franklin, Berlin*—I. Blau; *Universitaatsklinik Albert-Ludwigs-Uni-Freiburg, Freiburg*—C. Waller; *Universitatsklinikum Bonn, Bonn*—D. Wolf; **Hungary:** *Markosovszky Egyetemi Oktatokorhaz, Szombathley*—L.-J. Ivanyi; *Szegedi Tudomanyegyetem, Szeged*—Z. Borbenyi; *Bacs-kiskun Megyei Onkormanyzat Korhaza, Kecskemet*—G. Pajkos; *Fov Onk Egyesitett Szent* István és Szent *Laszlo Korhaz, Budapest*—T. Masszi; **Italy:** *Az Osp Universit Careggi—Univ Studi di Firenze, Firenze*—A.-M. Vannucchi and P. Guglielmelli; *Fondazione IRCC Policlinico S Matteo Univ degli Studi Pavia, Pavia*—M. Cazzola; *Az Sanit Osp Univ S Luigi Gonzaga di Orbassano Regione Gonzole, Univ degli Studi di Torino, Orbassano*—D. Cilloni; *AOU Policlinico Umberto I Univers La Spienza, Roma*—A. Tafuri and G. Alimena; *Presidio Ospedaliero S Bortolo ULSS 6 Vicenza, Vicenza*—F. Rodeghiero; *Az Osp Univ Consorziale Policlin di Bari Univ degli Studi, Bari*—G. Specchia; *AO Bianchi Melacrino Morelli—Presidio Ospedali Riuniti, Reggio Calabria*—F. Nobile; *Fondazione IRCCS Policlinico San Matteo, Pavia*—V. Rosti and G. Barosi; *Papa*

Giovanni XXIII Bergamo—A. Rambaldi; *Az Osp di Bologna Policlinico S Orsola–Malpighi Univ degli Studi, Bologna*—M. Cavo and M. Baccarani; *AO Osp di Circolo e Fond Macchi–Polo Univ Pr Osp di Varese, Varese*—F. Passamonti and D.D. Caramazza; *A Osped–Universit Policlinico Federico II Univ degli Studi, Napoli*—F. Pane; *Az Ospedariela Niguarda Ca' Granda, Milano*—E. Pungulino; **Korea:** *Severance Hospital, Seoul*—Y. Min; *Seoul St Mary's Hospital, Seoul*—B. Cho; the **Netherlands:** *Erasmus Medical Center, Rotterdam*—P.A.W. te Boekhorst; *Medische Spectrum Twente Enschede*—W.M. Smit; **Spain:** *Hospital del Mar Barcelona, Cataluna*—C. Besses; *Hospital Universitario Doctor Negrin Las Palmas de Gran Canaria, Las Palmas de GC*—M.-T. Gomez Casares; *Hospital Clinico Universitario Sanitiago De Compostela, Valencia, Comunidad Valeniana*—J.-C. Hernandez Boluda; *Complejo Hospitalario de Navarra, Pamplona, Navarra*—E. Olavarria Lopez; *Hospital 12 de Octubre, Madrid*—J. Martinez Lopez; *Hospital Virgen de La Victoria, Malaga, Andalucia*—M.-P. Queipo de Llano Temboury and S. Del Castillo; *Antes Hospital Juan Canalejo, La Coruna, Galicia*—C. Fernandez Lago; *Hospital Universitario de Salamanca, Salamanca, Castilla Y Leon*—J.-M. Hernandez Rivas; **Turkey:** *Ege University Medical Faculty Hospital, Izmir*—G. Saydam; *Hacettepe University Medical Faculty, Ankara*—I. Haznedaroglu; *Istanbul University, Istanbul Medical Faculty, Istanbul*—A. Yavuz; **United Kingdom:** *Guy's Hospital, London*—C. Harrison; *Cardiff University Hospital, Cardiff, Wales*—S. Knapper; *Royal Bournemouth Hospital, Bournemouth*—J. Chacko; **Russia:** *Research Institute of Hematology and Transfusiology of Federal Agency of High-Technology Medical Care, St Petersburg*—K. Abdoulkadyrov; *Institute of Cardiology and Endocrinology, St Petersburg*—A. Zaritsky; *Hematological Scientific Center of RAMS, Moscow*—M. Sokolova and N. Khoroshko; **Japan:** *University of Yamanashi Hospital, Chuo-city, Yamanashi*—K. Kirito; *Japanese Red Cross Medical Center, Shibuya, Tokyo*—K. Suzuki; *Osaka City University Hospital, Osaka-City, Osaka*—M. Hino; *Chiba University Hospital, Chiba-city, Chiba*—M. Takeuchi; *Japanese Red Cross Nagoya Daiichi Hospital, Nagoya, Aichi*—K. Miyamura; *Gunma University Hospital, Maebashi-City, Gunma*—H. Handa; *Keio University Hospital, Shinjuku-ku, Tokyo*—S. Okamoto; **Thailand:** *Siriraj hospital, Bangkok*—S.

Issaragrisil; **Argentina:** *Hospital Ramos Mejia CABA, Buenos Aires*—B. Moiraghi; **China:** *Jiangsu Province Hospital, Nanjing, Jiang Su*—J. Li; *Peking Union Medical College Hospital, Beijing, Beijing*—D. Zhou; *First Affiliated Hospital Zhejiang Medical University, Hangzhou, Zhejiang*—J. Jin

Supplementary Methods

Phlebotomy dependence was defined as ≥ 2 phlebotomies within the 24 weeks before screening and ≥ 1 phlebotomy within the 16 weeks before screening. The most distant and the most recent phlebotomy within the 24 weeks before screening must have been ≥ 4 weeks apart; patients were also considered to have met this criterion if they required a phlebotomy within the 16 weeks before screening and they exhibited a hematocrit (HCT) > 45% at screening.

The distribution of ruxolitinib doses received at week 32 were summarized as the maximum dose within a 2-week window of week 32 (ie, day 211 to 239). The mean total daily dose over time was summarized at the target day of each study visit (eg, at day 225 for the week 32 visit).

Patients with missing assessments that prevented the evaluation of the primary endpoint were considered nonresponders. A missing HCT assessment that was required to confirm HCT control (absence of phlebotomy eligibility) was presumed to mean that the patient had met the phlebotomy eligibility criterion. All data from scheduled and unscheduled assessments within the window were included in the analyses. To be considered as having HCT control (absence of phlebotomy eligibility) between weeks 8 and 32, patients could have no more than 1 missing HCT assessment at any of the scheduled visits between weeks 8 and 32, inclusive. Patients with > 1 missing HCT assessment at the scheduled visits between weeks 8 and 32 were considered to be primary endpoint nonresponders. Patients who discontinued the study before completion of week 32 visit assessments were considered nonresponders.

Patients with > 1 missing HCT assessment at the scheduled visits between weeks 40 and 48 were not considered to be durable HCT responders at 48 weeks. Patients with > 1 missing assessment at the scheduled visits between weeks 40 and 80 were not considered to be durable HCT responders 48 weeks after initial response.

Durability of Primary Response

Initial response could occur as early as the week 16 visit, if a spleen response and absence of phlebotomy eligibility were observed but no later than week 32. End of response was the date following week 32 of the first occurrence of 1 of the following.

- The first of 2 consecutive HCT assessments that confirmed phlebotomy eligibility
- Spleen volume assessment that was reduced by < 35% from baseline *and* ≥ 25% increased relative to the volume determined at the time of the best documented spleen response
- Death due to any cause
- Development of myelofibrosis as evidenced by bone marrow biopsy
- Development of acute myeloid leukemia as evidenced by bone marrow blast counts of ≥ 20% or peripheral blast counts of ≥ 20% lasting ≥ 2 weeks

Definition of an Inadequate Response to/Unacceptable Side Effects From Hydroxyurea

An inadequate response to hydroxyurea (HU) was defined as a dose ≥ 2 g/day or a maximum tolerated dose < 2 g/day resulting in at least 1 of the following.

- Need for phlebotomy to maintain HCT < 45%
- Platelet (PLT) count > 400 × 10^9/L and white blood cell (WBC) count > 10 × 10^9/L
- Failure to reduce splenomegaly extending > 10 cm below the costal margin by > 50%, as measured by palpation

Unacceptable side effects from HU were defined as at least 1 of the following.

- Absolute neutrophil count (ANC) < 1.0 × 10^9/L
- PLT count < 100 × 10^9/L or hemoglobin (Hb) < 100 g/L (ie, 10 g/dL) at the lowest dose of HU required to achieve a response

- Presence of leg ulcers or other unacceptable HU-related nonhematologic toxicities (such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis, or fever at any dose of HU), defined as Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 grade 3-4 or > 1 week of CTCAE version 3.0 grade 2, permanent discontinuation of HU, interruption of HU until toxicity resolved, or hospitalization due to HU toxicity

Dose Modifications

The starting dose was ruxolitinib 10 mg twice daily (BID) and could be titrated for safety and efficacy (minimum of 5 mg once daily and maximum of 25 mg BID). The dose of ruxolitinib could be increased in 5-mg BID increments for patients who met all of the following conditions.

1. Inadequate efficacy as demonstrated by at least 1 of the following.
    a. HCT ≥ 45% or HCT < 45% but ≥3 percentage points higher than the HCT obtained at baseline
    b. WBC count > upper limit of normal (ULN)
    c. PLT count > ULN
    d. Palpable spleen that is reduced by < 25% from baseline at week 4 or < 50% at subsequent study visits (ie, week 8 or beyond)
2. PLT count ≥ 140×10^9/L
3. Hb ≥ 12 g/dL
4. ANC ≥ 1.5×10^9/L

Dose adjustments of ruxolitinib were required for hematologic safety. Doses were decreased for any Hb level <10.0 g/dL and/or PLT count < 75×10^9/L. Dose reductions were allowed for grade 1 anemia (Hb level < lower limit of normal to 10.0 g/dL) and PLT count < 100×10^9/L if, in the Investigator's judgment, such a change was warranted given the rapidity and magnitude of the hematologic change.

Statistical Analyses

The statistical null hypotheses for the primary analysis were:

H0: $\pi_{\text{Ruxolitinib}} = \pi_{\text{Standard therapy}}$ versus H_1: $\pi_{\text{Ruxolitinib}} \neq \pi_{\text{Standard therapy}}$

where $\pi_{\text{Ruxolitinib}}$ and $\pi_{\text{Standard therapy}}$ are the responder rates at Week 32 for the primary endpoint in the ruxolitinib and standard therapy group, respectively. Responder rates were compared using exact Cochran-Mantel-Haenszel (CMH) test stratified by HU status (inadequate response to HU vs unacceptable side effects from) at 5% significance level and presented using 95% confidence intervals using Clopper Pearson exact method. While overall stratum-adjusted odds ratio was used as a measure of association between treatment and response (presented with 95% Wald confidence intervals).

Conditional on significance of the primary endpoint, the key secondary endpoints were compared using similar approach ensuring a family wise α-level was controlled at 0.05 using the Hochberg procedure.

Study Sponsorship and Sources of Funding

This trial is supported equally by Incyte and Novartis. Research conducted at the University of Florence was supported in part by Associazione Italiana per la Ricerca sul Cancro, grant #1005. MD Anderson receives a cancer center support grant from the NCI of the National Institutes of Health (P30 CA016672) that was used, in part, to support research conducted at the University of Texas MD Anderson Cancer Center.

Supplementary Results

Patients were enrolled in Argentina (n=4), Australia (n=11), Belgium (n=11), Canada (n=5), China (n=3), France (n=11), Germany (n=25), Hungary (n=15), Italy (n=43), Japan (n=18), the Netherlands (n=3), Russia (n=7), Korea (n=4), Spain(n=13), Thailand (n=1), Turkey (n=6), the United Kingdom (n=7), and the United States (n=35).

Efficacy

The proportions of patients randomized to ruxolitinib who achieved the primary efficacy endpoint were comparable for patients who entered the study with an inadequate response to HU and for those who had unacceptable side effects from HU (19.61% vs 22.03%, respectively). Sex and age did not affect the response rates in ruxolitinib-treated patients. In the ruxolitinib arm, 26.76% of patients (19 of 71) with baseline palpable splenomegaly < 10 cm achieved the primary efficacy endpoint compared with 10.81% of patients (4 of 37) with baseline palpable splenomegaly ≥ 10 cm. This observation was further explored post hoc by using a linear regression model on percent change in spleen volume at week 32 and a logistic regression model on HCT control at week 32, both adjusting for baseline spleen volume. No relationship between the primary response components and baseline spleen volume was observed.

Furthermore, 23 patients (ruxolitinib, n=9; standard therapy, n=14) were enrolled without palpable splenomegaly (but with a spleen volume meeting the protocol eligibility criteria). The primary endpoint was achieved in 2 patients (22.2%) randomized to ruxolitinib and no patients on standard therapy. Similarly, higher rates of spleen volume response and HCT control were achieved in patients randomized to ruxolitinib (55.6% and 44.4%, respectively) compared with patients randomized to standard therapy (0% and 14.3%).

The mean change from baseline Janus kinase 2 V617F allele burden at week 32 was a decrease of 12.16% in the ruxolitinib group (n=92) and an increase of 1.18% in the standard therapy group (n=80).

The allele burden steadily decreased over time in the ruxolitinib group, with a maximal mean decrease from baseline of 34.73% at week 112 (n=22). Changes in C-reactive protein (CRP) levels were also assessed. Patients had median CRP values of 1.85 (ruxolitinib) and 1.4 (standard therapy) μg/mL at baseline. At week 32, the ruxolitinib group median CRP values had decreased to 0.46 μg/mL (75% decrease), whereas the standard therapy group median CRP values had increased to 1.9 μg/mL (36% increase); this is indicative of a reduction in inflammation by ruxolitinib treatment, with the standard therapy group having indications of a persisting inflammatory state.

Figure S1. Mean Ruxolitinib Dose Over Time.

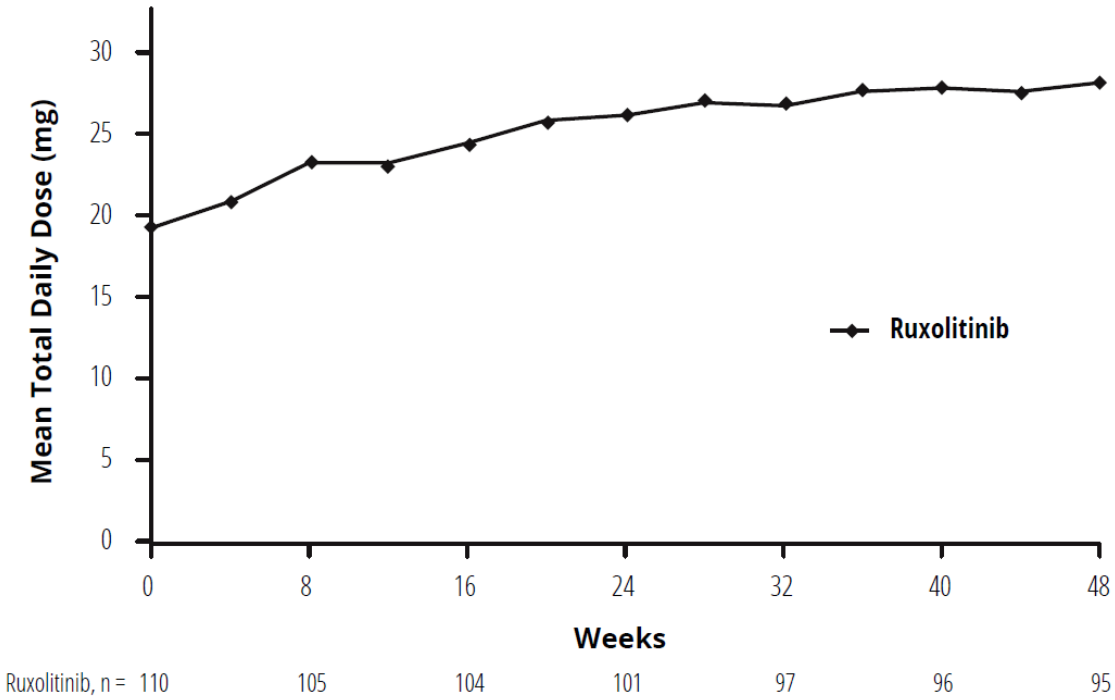
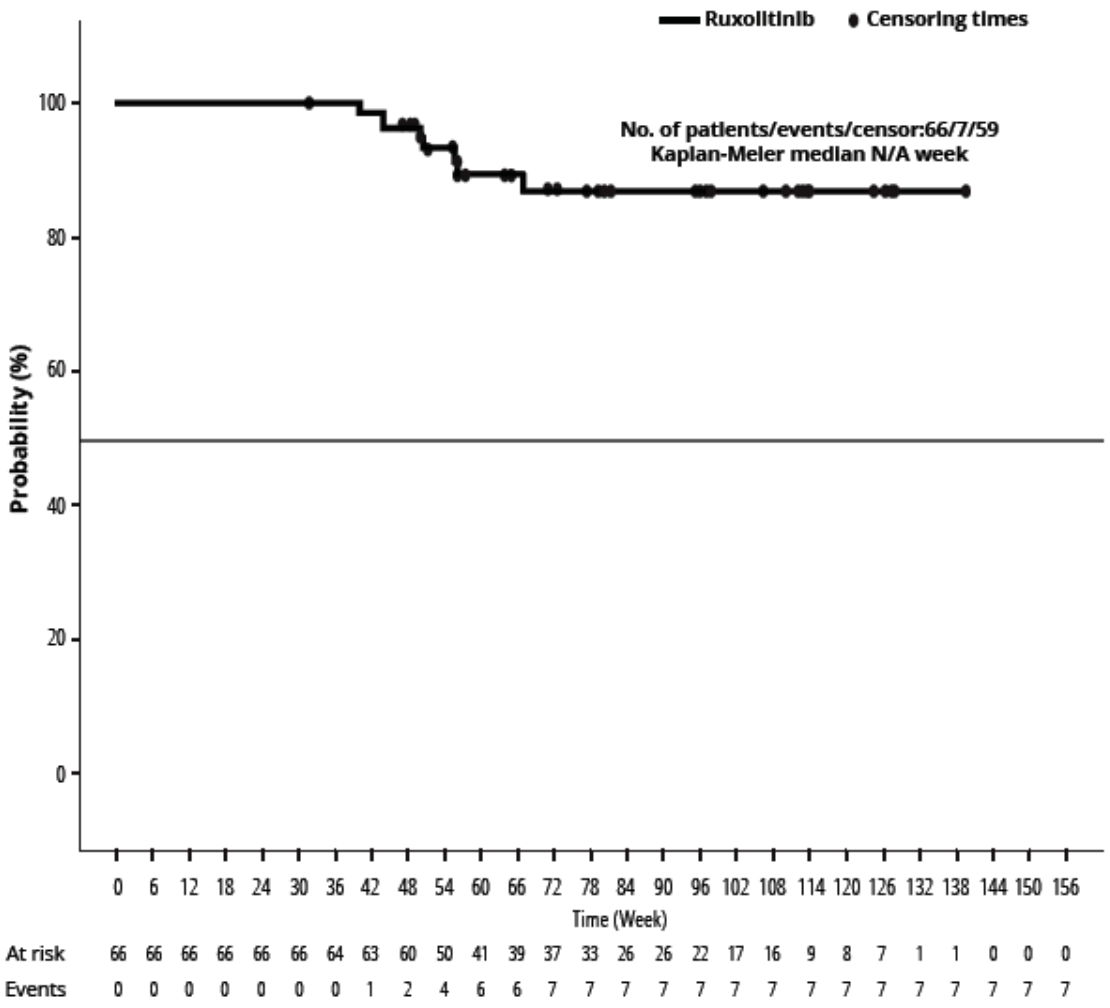


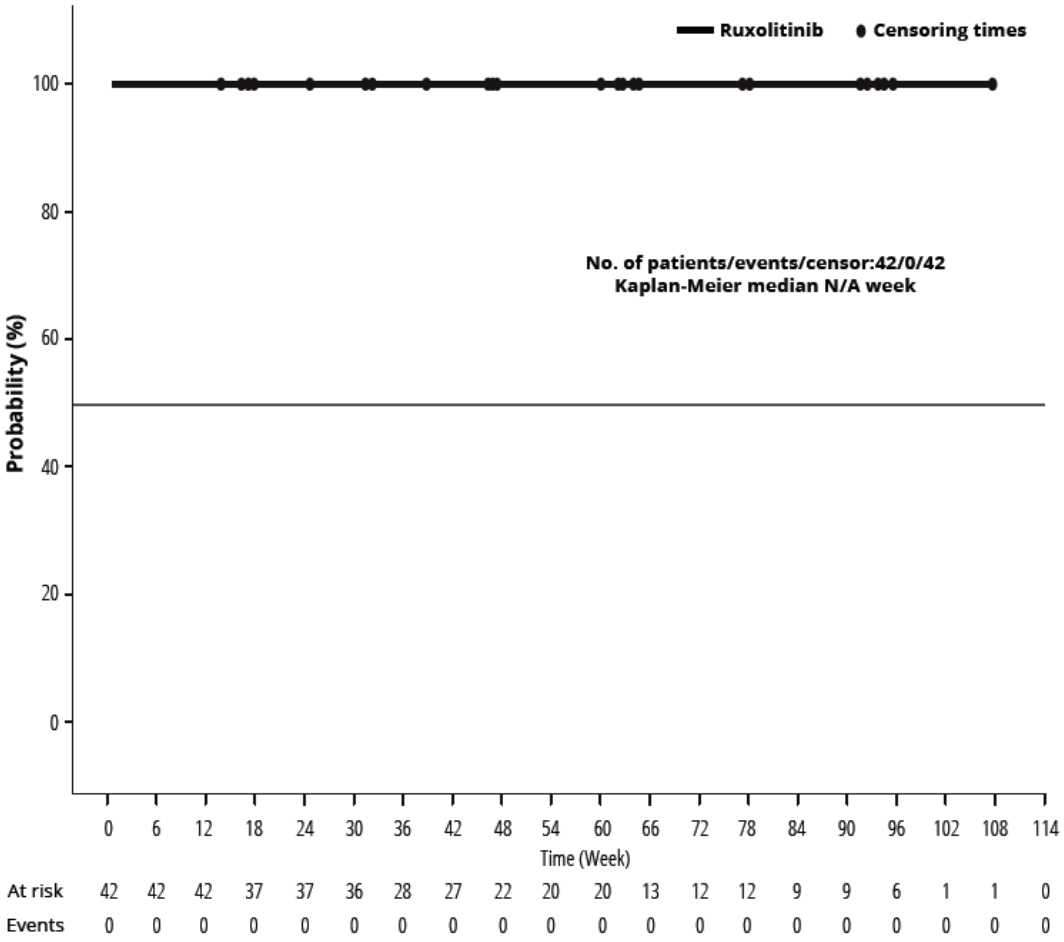
Figure S2.

A. Duration of HCT control[a]



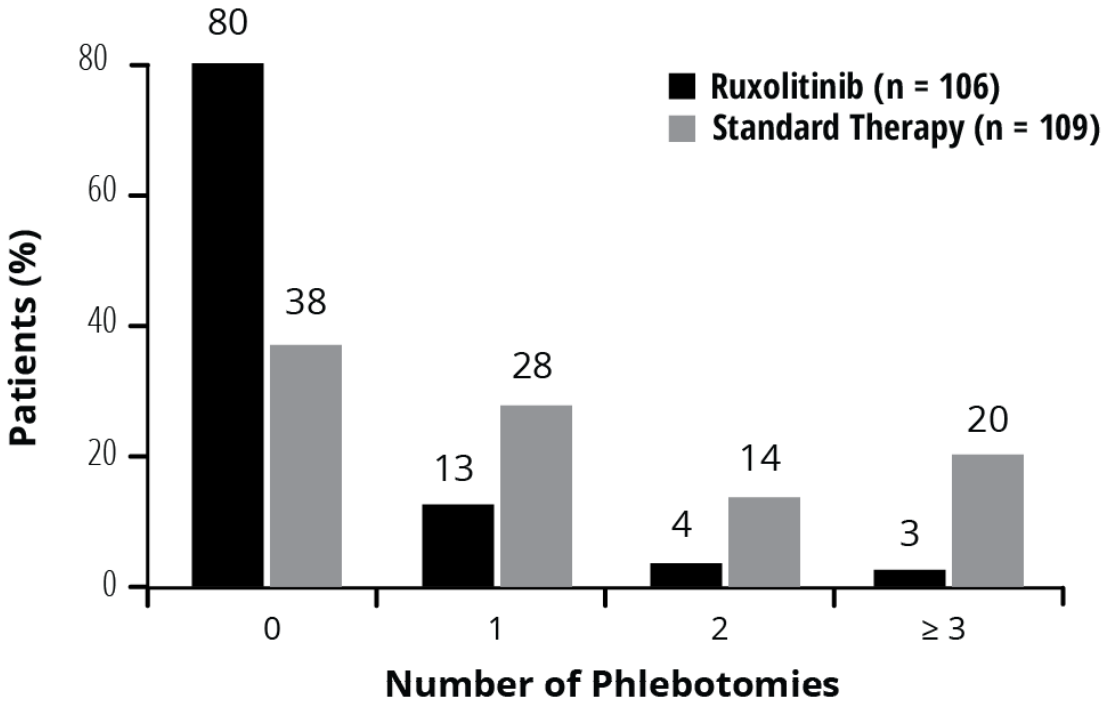
[a] Duration of hematocrit (HCT) control is defined as the time from the first occurrence of absence of phlebotomy eligibility until the date of first documented progression.

B. Duration of Spleen Volume Reduction[a]



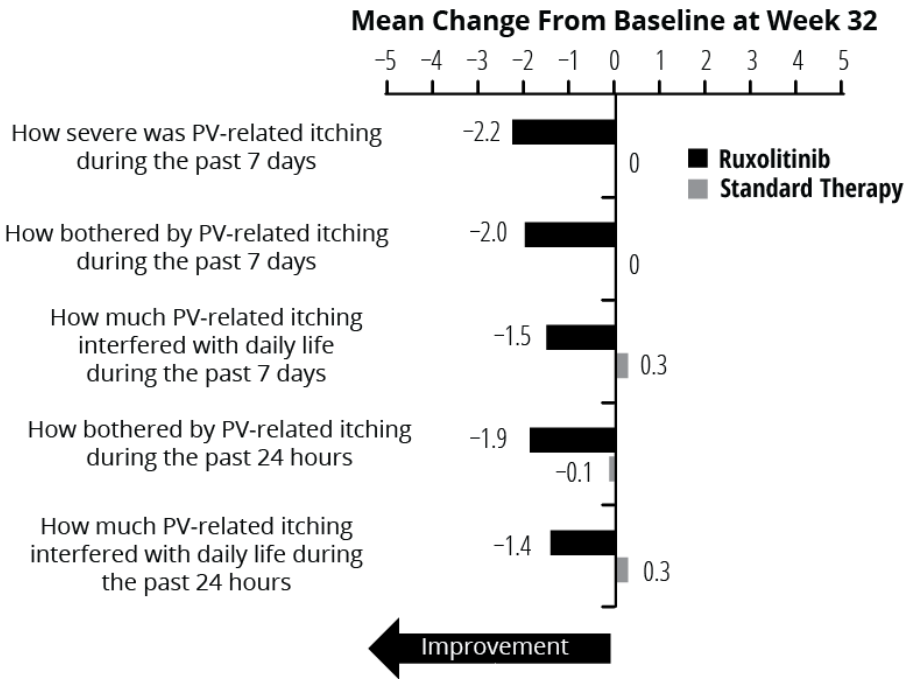
[a] Duration of spleen volume reduction is defined as the time from the first occurrence of ≥ 35% reduction from baseline in spleen volume until the date of first documented progression.

Figure S3. Rates of Phlebotomies From Week 8 to 32.[a]



[a] Includes patients who did not discontinue randomized treatment prior to week 8.

Figure S4. Mean Change From Baseline on the Pruritus Symptom Impact Scale[a] at Week 32.

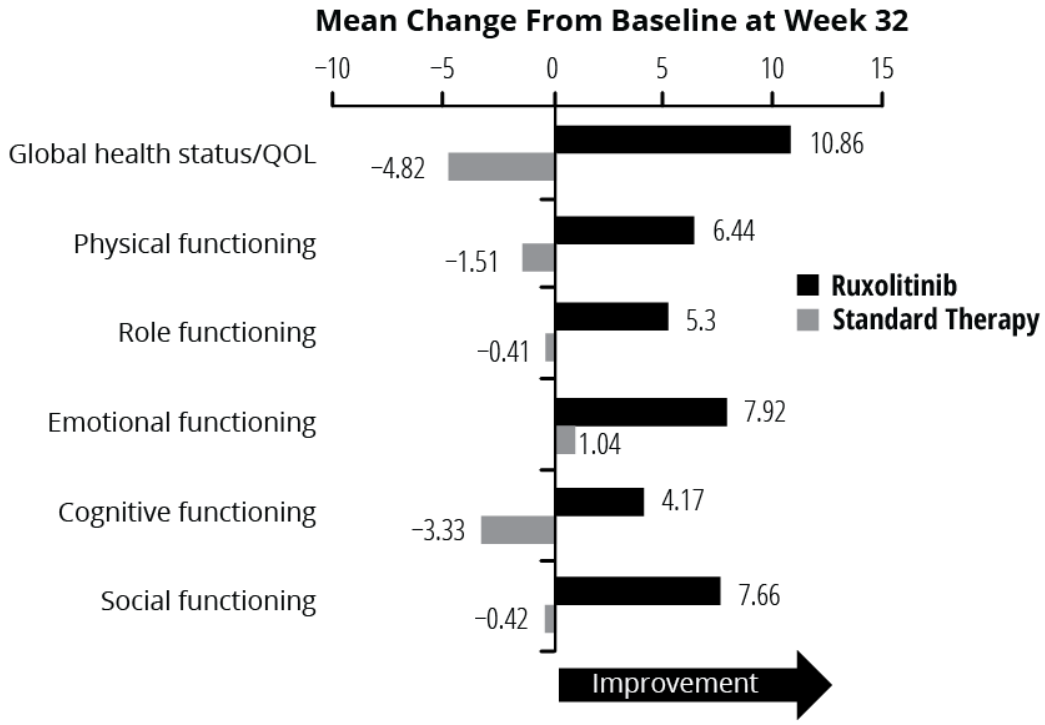


[a] Includes patients with assessments at both baseline and week 32. Patients responded to each question on a scale of 0 (not at all) to 10 (worst imaginable).

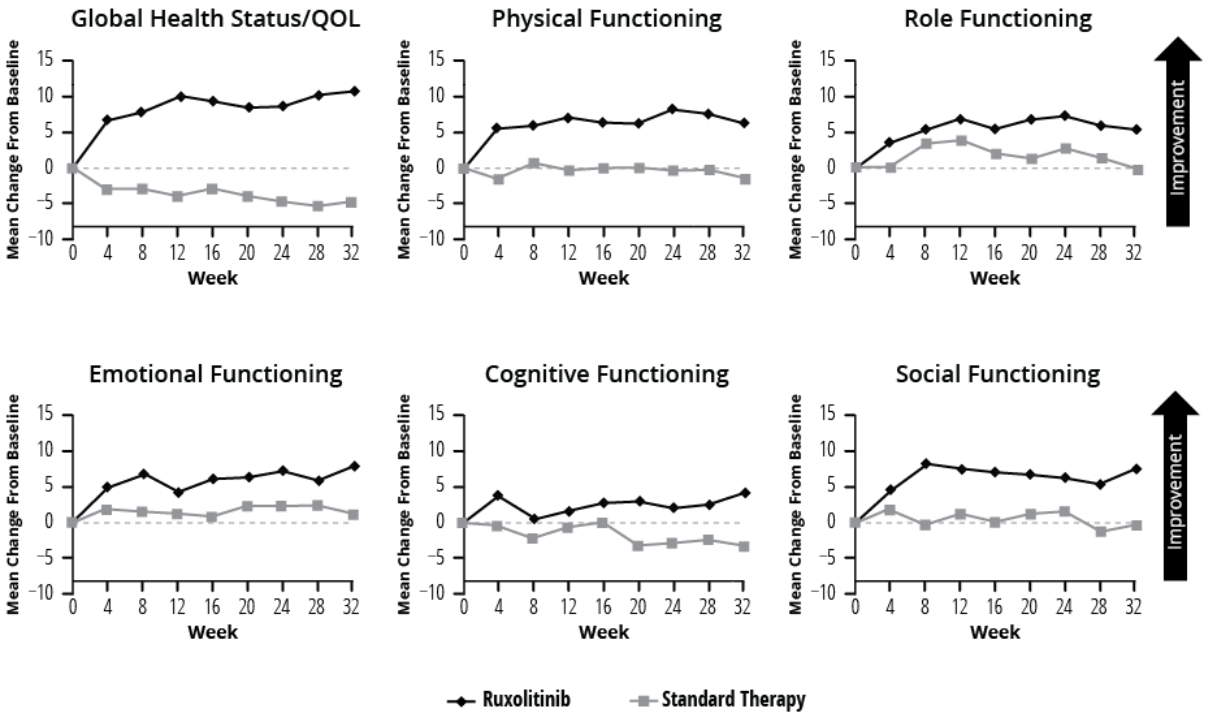
PV, polycythemia vera.

Figure S5.

A. Mean Change From Baseline EORTC QLQ-C30 QOL and Functioning Scores at Week 32



B. Mean Change From Baseline EORTC QLQ-C30 QOL and Functioning Scores Over Time



EORTC QLQ-C30 QOL, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

Figure S6. Patient Global Impression of Change at Week 32.

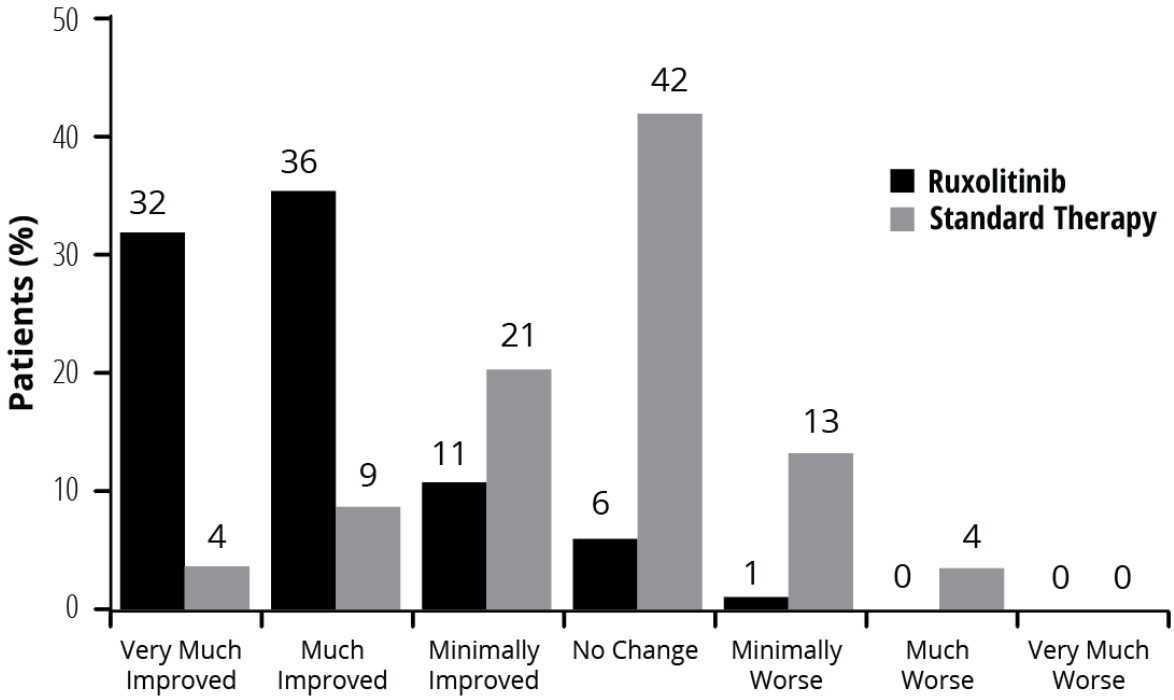
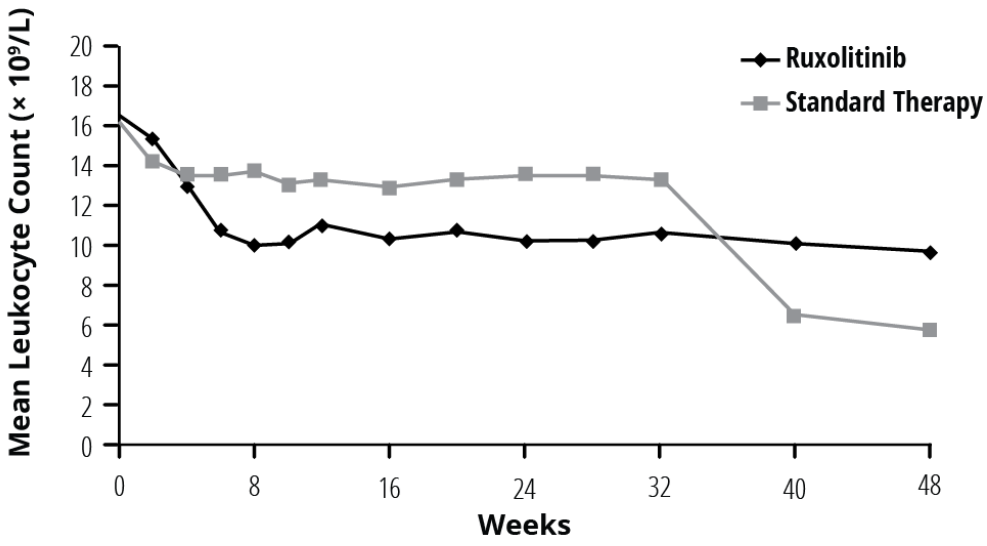


Figure S7. Leukocyte Count Over Time.



Ruxolitinib, n =	110	106	103	100	96	95	95
Standard Therapy, n =	111	107	105	104	87	6	5

Table S1. Patient Disposition

n (%)	Ruxolitinib (n = 110)	Standard Therapy (n = 112)[a]
Continued on randomized treatment	93 (84.5)	3 (2.7)
Discontinued randomized treatment	17 (15.5)	108 (96.4)
Primary reason for discontinuation		
Adverse event	4 (3.6)	2 (1.8)
Lack of efficacy	0	98 (87.5)
Disease progression	5 (4.5)	1 (0.9)
Patient decision	6 (5.5)	5 (4.5)
Physician decision	2 (1.8)	2 (1.8)

[a] One patient withdrew consent and was not treated on study.

Table S2. Efficacy by Initial Treatment in the Standard Therapy Arm

	n (%)	Spleen Volume Reduction ≥ 35%	HCT Control Without Phlebotomy
All Standard Therapy	**112 (100)[a]**	**1 (0.9)**	**22 (19.6)**
HU	66 (58.9)	1 (1.5)	15 (22.7)
IFN/pegylated IFN	13 (11.6)	0	4 (30.8)
Anagrelide	8 (7.1)	0	1 (12.5)
Pipobroman	2 (1.8)	0	1 (50.0)
IMIDs	5 (4.5)	0	0
No medication[b]	17 (15.2)	0	1 (5.9)

[a] One patient was randomized but did not receive study drug.

[b] Patients who received no drug as their standard therapy may have received phlebotomy for HCT control and low-dose aspirin unless contraindicated.

HCT, hematocrit; HU, hydroxyurea; IFN, interferon; IMID, immunomodulatory drug.

Table S3. Frequent (> 10%) New or Worsened Nonhematologic Laboratory Abnormalities

	Ruxolitinib		Standard Therapy	
Laboratory Abnormality	**All Grade %**	**Grade 3/4 %**	**All Grade %**	**Grade 3/4 %**
GGT (high)	46.4	7.3	21.6	3.6
Cholesterol (high)	42.7	0	6.3	0
Bicarbonate (low)	37.3	0	31.5	0
Lipase (high)	31.8	6.4	17.1	2.7
ALT (high)	31.8	0.9	10.8	0
AST (high)	28.2	0	18.0	0.9
Creatinine (high)	28.2	0	10.8	0
Glucose (low)	26.4	0	22.5	0
Glucose (high)	25.5	2.7	17.1	2.7
Potassium (high)	21.8	7.3	17.1	3.6
Triglycerides (high)	20.9	0	6.3	0
Urate (high)	18.2	2.7	29.7	9.9
Calcium (low)	17.3	1.8	14.4	0
Bilirubin (high)	15.5	1.8	13.5	1.8
Alkaline phosphatase (high)	15.5	0	6.3	0
Calcium (high)	14.5	0	2.7	0
Direct Bilirubin (high)	10.0	0.9	6.3	0.9

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, Gamma Glutamyl Transferase;

Table S4. Adverse Events Adjusted for Exposure to Study Medication (rates ≥ 10 per 100 patient-years)

Events per 100 Patient-Years' Exposure	**Ruxolitinib**		**Standard Therapy**	
Patient-year exposure	170.0		72.8	
	All grade, rate	**Grade 3/4, rate**	**All grade, rate**	**Grade 3/4, rate**
Any preferred term	64.7	28.8	145.6	44.0
Anemia	15.9	1.2	5.5	0
Thrombocytopenia	7.6	2.4	16.5	2.7
Diarrhea	12.4	0	12.4	1.4
Abdominal pain	7.1	1.2	17.9	0
Fatigue	11.2	0	23.3	4.1
Asthenia	5.9	1.2	16.5	0
Nasopharyngitis	7.6	0	12.4	0
Arthralgia	7.6	0	11.0	1.4
Headache	13.5	1.2	28.8	1.4
Dizziness	8.8	0	15.1	0
Pruritus	11.2	0.6	34.3	5.5
Night sweats	5.9	0	12.4	0

Table S5. Thromboembolic Events up to Week 32

Patients, n (%)	Ruxolitinib (n = 110)		Standard Therapy (n = 111)	
	All Grade	**Grade 3/4**	**All Grade**	**Grade 3/4**
All thromboembolic events	1 (0.9)	1 (0.9)	6 (5.4)[a]	2 (1.8)[a]
Portal vein thrombosis	1 (0.9)	1 (0.9)	0	0
Myocardial infarction	0	0	1 (0.9)	1 (0.9)
Deep vein thrombosis	0	0	2 (1.8)	1 (0.9)
Pulmonary embolism	0	0	1 (0.9)	1 (0.9)
Splenic infarction	0	0	1 (0.9)	0
Thrombophlebitis	0	0	1 (0.9)	0
Thrombosis	0	0	1 (0.9)	0

[a] One patient in the standard therapy group had both myocardial infarction and pulmonary embolism.